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(54) Title: THE PREPARATION OF TOPICAL REGIONAL COMPOSITIONS FOR THE RELIEF OF PAIN

(57) Abstract

A safe and relatively simple method is presented for the preparation of topically applied compositions used for the treatment of pain, especially sympathetically mediated pain, regardless of cause, in persons of either sex. The method utilizes the periodic application of topical compositions containing three classes of therapeutically effective agents prepared in suitable bases, to the skin areas affected by the pain. The three classes of therapeutic active agents are NMDA receptor antagonists, anticholinergic agents and sympathetic blocking agents. Each can be used alone or in combinations. The method provides significant pain relief which begins within minutes and lasts greater than 2 hours. The prepared compositions are non-toxic and have minimal side effects. No habit forming or addicting medications are used as therapeutically active ingredients. The prepared compositions can be self-administered or can be administered by another person at home or in any locale. Finally, the use of this method provides a previously unavailable means of treating patients with pain, especially sympathetically mediated pain.

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THE PREPARATION OF TOPICAL REGIONAL COMPOSITIONS FOR THE RELIEF OF PAIN

BACKGROUND: FIELD OF INVENTION

The field of this invention is the process for the preparation of topical compositions used for the treatment of pain, especially pain caused by nerve injury or sympathetically mediated pain. More specifically, the field of this invention relates to n-methyl d-aspartate (NMDA) receptor antagonists, anticholinergic agents, and sympathetic blocking agents, administered topically in a gel or cream base composition, and effective for the relief of pain due to nerve injury or damage.

Sympathetically mediated pain (SMP) is a type of pain in which overactivity of the sympathetic nervous system plays a crucial role. It includes the syndromes of reflex sympathetic dystrophy, causalgia, neuropathic pain secondary to nerve injury, and pain from neuromas. It encompasses all neurogenic pain that is not central and is related to a nerve injury regardless of the cause.

Sympathetically mediated pain (SMP) is a major worldwide epidemic condition. There are greater that 6 million Americans suffering from SMP today. SMP can be so severe that it has been compared to being ten times the intensity caused by childbirth. It is, overall, the most common cause of pain-induced suicide in the US. It is virtually incurable if treatment is initiated greater than 6 months after the disease has been triggered. However, diagnosis in these six months is unusual because, early in the condition, it is so difficult to make.

The signs and symptoms of sympathetically mediated pain are varied. It occurs most often in the limbs but virtually any part of the body can be affected. It can occur at any age, but is often unrecognizable in the very young and is rarely diagnosed at all in its early stage in the absence of a high degree of suspicion. A special bone scan called the triple phase bone scan is diagnostic in some cases in later stages.

There are a number of different types of pain associated with nerve injury or SMP. These types are usually defined by their subjective effects. The specific types of pains which are included in the field of this invention are defined as follows:

Allodynia: pain due to a stimulus that normally does not cause pain, for example as the light touch from air passing over skin.

Hyperpathia: A painful syndrome characterized by increased reaction to a stimulus, especially a repetitive stimulus, as well an increased threshold.

Hyperesthesia: An increased sensitivity to normal stimulation excluding the special senses.

Hyperalgesia: An increased response to a stimulus that is normally painful.

Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked.

Paresthesia: An abnormal sensation, whether spontaneous or evoked.

Deafferentation Pain: Pain due to loss of sensory input into the central nervous system, as occurs with avulsion of the brachial plexus or other types of lesions of the peripheral nerves or due to pathology of the central nervous system.

Anesthesia Delorosa: Pain in an area or region that is anesthetic (anesthetic means absence of all sensations).

A classical patient with SMP exhibits hyperpathia, allodynia, swelling, and an electrical shock type parasthesia pain in the limbs. Many SMP patients also experience the other types of pain defined above. The compositions of this invention result in significant relief of all types of SMP defined above.

The field of this invention is the preparation of compositions utilized in the topical treatment of these types of pain.

BACKGROUND: DESCRIPTION OF PRIOR ART

The prior and present treatment of sympathetically mediated pain (SMP) or pain due to nerve damage is directed towards relief of subjective symptoms. Currently, there are several categories of treatments utilized.

I. Oral medication

1. Standard analgesic medications, including morphine and other opiates, which are generally almost completely ineffective for this type of pain.

2. Ganglionic blocking agents, such as phenoxybenzamine, are more effective than standard analgesics. However, in doses necessary to achieve even minimal pain relief, they can produce totally disabling side effects, such as a sufficiently sharp fall in the blood pressure to render the patient unable to stand or walk without fainting.

3. Tricyclic antidepressants, such as amitriptylline, are mildly effective in about 20% of cases but cause drowsiness.

4. Anti-convulsants, such as carbamazepine, are partially effective in about half of the cases in the relief of electric

shock type lancinating parasthesia pain but offer little or no relief from the major burning type of pain.

5. Adrenergic blocking agents, such as yohimbine and terazosine, are only sporadically and temporarily effective. The low blood pressure caused by these agents make their use limited.

II. Nerve Blocks: Epidural nerve blocks or sympathetic nerve blocks, are invasive procedures using local anesthetics or nerve sclerosing agents, such as phenol or alcohol. Such nerve blocks temporarily or permanently interrupt nerve conduction to and from the painful area. The methods are invasive and temporary, although the analgesic affects may last as long as four to six weeks. However, these methods require a physician pain specialist to inject the patient and are usually performed in an expensive, often inconvenient, hospital setting. Injections using sclerosing agents are fraught with danger, including the formation of neuromas, which can result in worse pain than was originally present. Nerve sclerosing agents are tried as a last resort but rarely are successful.

III. Surgical Procedures: Many have been devised wherein the SMP patient would be subjected to a severing of the spinal cord or of nerves, and even ablation of parts of the brain. However, in the long term, these methods invariably end up with poor results and worse

pain. Other surgical procedures costing upwards of 20 thousand dollars each include permanent implantation of peripheral nerve stimulators, spinal cord stimulators, and deep brain stimulators. Aside from being very expensive, these implants are risky and the results are poor.

IV. Topical Treatments: There are currently a limited number of topical treatments available. These agents offer only minimal and short term , usually less than one hour, of pain relief.

1. Geranium oil (applicants patent No. 5,260,313): The severe pungent odor of strong geranium oil discourages frequent use of this medication. In addition, the relief is generally limited to 2 hours or less.

2. Topical local anesthetics or salicylates: Pain relief occurs in fewer than 25% of the SMP patients. Even then, only half of the pain is relieved.,

3. Capsaicin (Cayenne Pepper Extract): This agent applied topically results in an initial burning sensation that discourages the SMP patient from its further use. It provides substantial pain relief for only a small number of SMP patients and then not until after one week of repetitive use.

V. Miscellaneous Other Methods: Although these techniques are occasionally successful, pain relief results in SMP is considered minimal. These methods include, but are not limited to, guided imagery techniques, acupuncture, hypnosis, physical therapy, and biofeedback.

OBJECTS AND ADVANTAGES

The object of the invention is to provide a process for the preparation of a composition that results in a relatively simple topical method of pain relief in patients with all types of pain, especially sympathetically mediated pain (SMP) or pain due to nerve damage, including peripheral neuropathies.

It is another object of the invention to provide a method of preparation of a composition that results in pain relief in SMP patients after the application of topical substances.

An additional object of the invention is to provide a composition for pain relief which will last longer than two hours. A further object of the invention is to provide a composition for pain relief which will last longer than 2 hours and which can be self-administered.

A still further object of the invention is to provide a method of preparation of this type of topical self administered pain relief utilizing non toxic agents with minimal side effects.

A yet further object of the invention to provide a method of preparation of this type of non-toxic, minimal side effect, topical medication for the treatment of patients with pain, especially nerve injury pain or sympathetically mediated pain, which is non-addictive and non-habit forming.

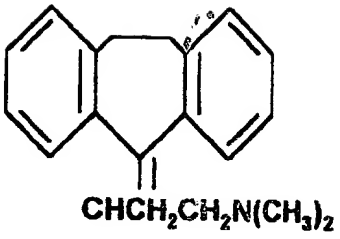
Still further objects and advantages will become apparent through a consideration of the ensuing description.

PREFERRED EMBODIMENT: DESCRIPTION AND OPERATION

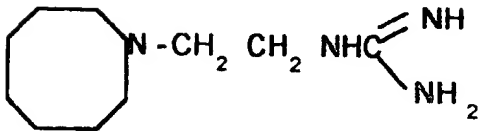
The present invention relates to the methods of preparation of the compositions used as topical regional treatments for the purpose of eliminating pain, especially pain due to nerve damage (which is referred to as sympathetically mediated pains or SMP). These compositions contain as their principle and active therapeutic agent a drug from one (or more) of the following 3 classes of agents;

Class 1. The non-competitive n-methyl d-aspartate ion channel blocking agents, which will be referred to hereafter as NMDA receptor antagonists, such as ketamine (patent number 3.254.124) and dextromethorphan (patent number 2, 676,177). Ketamine is currently used as a general anesthetic and primarily administered parenterally by injection. Dextromethorphan is used primarily as a cough suppressant.

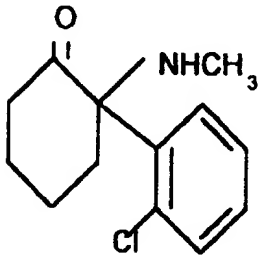
Class 2. The anticholinergic agents, an example of which are tricyclic antidepressants such as amitriptylline (patent number 3.205.264). Amitriptylline is currently primarily prescribed for the oral treatment of depression. It is secondarily prescribed for use as an oral analgesic. It is also available parenterally.



Amitriptylline



Guanethidine



Ketamine

CHEMICAL STRUCTURE

Class 3. Sympathetic blocking agents such as guanethidine. (patent numbers 2.928.829, 3.006.913, and 3.055.882) This group of drugs is currently generally prescribed for the treatment of peripheral vascular disorders and hypertension. These agents are available by both the parenteral and oral routes.

None of the agents in any of the above three classes is currently available nor prescribed for use by topical administration.

Preparation of Topical Compositions:

To prepare a topical composition, one or more of the active therapeutic agents from the three classes above is directly mixed with a suitable topical base. The efficacious and used most commonly base in our studies is a lecithin matrix gel. The efficiency of lecithin, a matrix base, is attributed to its ability to enhance transport of the active therapeutic agent across the dermis and into the tissues below so as to exert the effects of these agents on the nerves in the region below where it is applied.

The main ingredients used to make the matrix gel are pure soybean lecithin granules and liquid octylpalmatate. The liquid octylpalmatate and ground lecithin are mixed at room temperature in a proportion of 60% lecithin to 40% octylpalmatate. For example, 1 kilogram of lecithin is added to 600cc of octylpalmatate. This mixture is then placed in a large commercial-type blender and blended together to the point where the whole mixture becomes liquefied. Even though granules of lecithin will still be seen floating around in

the mixture, the whole mixture should appear to be in an almost total liquid state. This liquid is then transferred to 500cc beakers which are placed on standard magnetic stirrers and allowed to stir at half speed undisturbed for 24 hours. At the end of the 24 hours the remaining lecithin granules will have completely liquefied, leaving a dark brown homogenous liquid of light oily texture.

The active therapeutic agent is then added to the liquid gel. For example, injectable ketamine, 50mg per ml, is added to the lecithin gel. For every 90ml of the now liquefied lecithin, 10ml of ketamine is added. By weight, the added 10ml of ketamine equals 500mg, resulting in 500mg of ketamine per 100cc of the 0.5% topical composition.

The liquefied lecithin tends to thicken and gel when additional water or other liquid is added, a reverse of the expected effect. As the 500mg of ketamine is commercially delivered in a 10cc liquid base, when it is added to the lecithin and stirred, the lecithin will begin to increase in density and gel. When a thicker gel is desired, water is added, a few milliliters at a time. The final thickness of the gel depends on how much additional water is added. The more water, the thicker the gel will become. In the example presented, the liquid ketamine is added so as to create a gel of optimal density for use by our patients. The end point or target density of the gel optimally is equal to that of commercial soft margarine.

In the preparation of a 0.05% tricyclic antidepressant (amitriptylline) lecithin composition, 5ml of liquid injectable amitriptylline (10mgm/ml) or five finely crushed 10 mgm amitriptylline tablets are utilized. The powdered tablets are placed in liquid solution by dissolving them in 2cc of distilled water. The 5ml of injectable liquid or dissolved tablets is then added to 95ml of liquefied lecithin so as to make 100cc of the topical amitriptylline composition. The method of preparation of the lecithin base for the amitriptylline topical composition is performed in the same manner as described in the preparation of the ketamine composition example above with the exception, naturally, of substituting the prescribed dosage of amitriptylline for ketamine.

In the preparation of a .05% guanethidine-lecithin composition five finely crushed 10mgm guanethidine tablets are utilized. The powdered tablets are then dissolved in 5cc of distilled water and added to 95cc of lecithin liquid so as to prepare a .05% guanethidine-lecithin composition. The method of preparation of the guanethidine lecithin base is the same as described for the ketamine composition example above other than, naturally, substituting the prescribed dosage of guanethidine for ketamine in the composition.

Instead of the lecithin base, it is also possible to use 99% pure aloe vera gel or any standard, medicinal, or cosmetic base including, but not limited to, cocoa butter, aquafor, petroleum jelly and most cold creams. The oil-based gels, overall, have a more rapid onset of action as well as being more cosmetically palatable to the patients.

The concentrations of the active therapeutic agents described above were, overall, the most effective in our studies. However, other concentrations may be more effective or less effective for individual patients.

Method of Application:

In applying these compositions to the skin, for maximum effectiveness and increased absorption, the area to which the composition is to be applied is first cleansed with an astringent, such as a standard commercial antiseptic, alcohol or witchhazel astringent. The area is then allowed to dry for a few seconds. Next, the prepared topical composition is applied to the complete target area of the skin (the painful area) and gently, but firmly, massaged in with the fingertips until all visible gel or cream has been absorbed.

The volume of gel or cream utilized naturally depends on the surface area of the patient's pain. One to ten teaspoons may be utilized in order to obtain the desired pain relief. One teaspoon may be used for a smaller pain-affected area and up to ten teaspoons may be applied for larger pain-affected areas.

Response:

Typically, the initial application of any one of these compositions to any area of the body exhibiting pain produces an initial fleeting feeling of numbness, similar to a topical anesthetic being applied to the skin. No adverse effect will occur to either the patient or to the bare fingered applicator (if

composition is not self-applied) when the .05% ketamine composition is used as the active therapeutic agent. When .05% amitriptylline is the active agent in the composition, the composition may produce a dryness of the mouth and some blurriness of vision. A person applying the topical cream or gel may be protected to avoid such dry mouth by wearing rubber gloves or a finger cot.

The guanethidine compositions occasionally result in headaches due to cerebral vasodilatation, and may occur in persons prone to migraines or vascular headaches (including any person applying the gel). Guanethidine gel must not be administered by migraine/vascular headache prone individuals unless they wear protective hand-covering. Furthermore, guanethidine gel or cream is relatively contraindicated in migraine/vascular headache prone patients or patients who are in shock, as the guanethidine may result in a severe headache and a significant lowering of blood pressure.

Mechanism of Action:

The mechanism of action of topical ketamine is believed to be similar to a long acting local anesthetic, thereby effectively blocking the underlying nerves. To date, however, the mechanism of action of topically applied ketamine acting regionally has not been fully determined.

The mechanism of action of the amitriptylline compositions is presumed to be due to the anticholinergic action of the tricyclic antidepressant. Once the antidepressant (or one of the other anticholinergics) passes through the

dermis it acts by blocking acetylcholine, a neurotransmitter. This prevents the transmission of impulses in the A-delta and C pain fibers, thereby resulting in pain relief.

Guanethidine in the topical composition passes into underlying adrenergic neurons resulting in an adrenergic blockade to occur. This prevents the transmission of impulses in the A-delta and C pain fibers. The topical guanethidine further inhibits or interferes with the release or distribution of the chemical mediator (presumably norepinepherine) at the sympathetic neuro- effector junction.

Serum blood levels of patients treated with compositions containing the active agents, 0.5% ketamine, 0.05% amitriptylline, and 0.05% guanethidine, respectively, were done at 5, 15, 30, 45, 60, 120 minutes following application of the compositions to eight different sites on each patient's body. The size of the sites varied from smaller than a quarter to an area equal to the patients entire back. No detectable blood levels of any of the compounds were ever detected.

The general mode of action of these topically applied compositions is referred to as topical regional. This refers to their action, which is restricted to the region below the surface where the application has occurred. In using topical regional routes of administration, the volume of drug absorbed systemically is so minimal that there is never a detectable blood level with standard blood testing laboratory equipment.

Following application of the topical composition the duration of significant pain relief was determined to be 2 to 24 hours. The composition may be reapplied as needed when the pain returns. The duration of pain relief was not dependent upon the severity of the patient's symptoms prior to the application.

The study in the following pages further illustrates the present invention. It will be apparent to those skilled in the art that only the preferred embodiment has been described in the preceding and in the following example and that there are various modifications and alterations which fall within the scope of this invention and are intended to be covered by the claims appended hereto.

STUDY COMPARING EFFICACY OF TOPICAL COMPOSITIONS CONTAINING THERAPEUTICALLY ACTIVE AGENTS ON RELIEF OF SYMPATHETICALLY MEDIATED PAIN

Introduction

The purpose of this study was to evaluate and compare the safety and efficacy in the application of five topical compositions prepared with three active ingredients and applied singly or in combinations for the purpose of relief of sympathetically mediated pain (SMP).

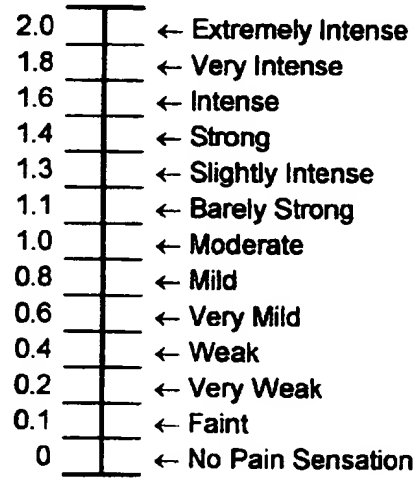
Materials and Methods

The study size was a total of thirty four volunteer subjects; fifteen female and nineteen male volunteer subjects. Their ages ranged from 29 to 84 with a mean of 52 years of age. All subjects were diagnosed with severe sympathetically mediated pain. Their demographics are illustrated in table 1.

Three different therapeutically active agents were utilized, alone or in combination, in preparations of lecithin matrix gels. The contents of these compositions were as follows:

1. Placebo (with no active ingredients)
2. Compositions containing Ketamine 0.5%
3. Compositions containing Amitriptylline 0.05%
4. Compositions containing Guanethidine 0.05%
5. Compositions containing a combination of Ketamine 0.5% and Amitriptylline 0.05%
6. Compositions containing a combination of Ketamine 0.5% and Guanethidine 0.05%

A different compositions was applied each treatment day to the area of maximum pain. The patients were asked to indicate the level of their pain immediately prior to the application of the compositions, and then at intervals of 5, 10, 15 minutes, 1, 2 and 3 hours after receiving treatment. Pain intensity was measured using the scale below.



Each patient was asked to choose the word that best described how the pain felt. The number corresponding to that word was then used to tabulate the intensity of the pain and for statistical analysis.

2 characteristic types of sympathetically mediated pain were tested;

1. Pain at rest.
2. Response to light touch (allodynia, hyperaesthesia, hyperpathia). Light touch was measured by stroking the skin over the painful area with a cotton swab.

Patients were questioned as to their pain intensity at 5 minute intervals for 15 minutes and then at 1, 2 and 3 hours.

SIGNIFICANT PAIN RELIEF WAS DEFINED AS >50% PAIN RELIEF SUSTAINED GREATER THAN 2 HOURS. For example, if a given patient rated his pain immediately prior to application of the compositions as "very intense", he would get a 1.8 score per the scale. In order for him to be placed in the category defined as "significant pain relief", he would have to judge his pain following application below 0.9, i.e., between "mild" and "no pain sensation" on the scale.

The entire study was performed under double blind conditions in that neither the subject nor the observers knew the contents of the topical compositions being applied. The study was conducted over five weeks with patients receiving treatment twice weekly with at least two days between treatments.

TOPICAL COMPOSITIONS STUDY: SUMMARY OF RESULTS

Total number of patients treated: 34 patients

Average age of patients treated: 52 years of age

1. **REST PAIN** - Constant uninterrupted pain without stimulus

Treatment	Percentage Patients with >50% Pain Relief		
	At 5 Minutes	At 2 Hours	At 3 Hours
A. Ketamine 0.5%	64.7	82.4	61.8
B. Amitriptylline 0.05%	32.4	50.0	32.4
C. Guanethidine 0.05%	5.9	8.8	2.9
D. A + B	82.4	97.1	97.1
E. A + C	79.4	88.2	82.4
F. Placebo	0	0	0

Treatment	Percentage Patients with 0 Pain Relief
A. Ketamine 0.5%	0
B. Amitriptylline 0.05%	5.9
C. Guanethidine 0.05%	11.8
D. A + B	0
E. A + C	0
F. Placebo	94.1*

Treatment	Time of Onset of Pain Relief (Patient Percentage)		
	5 Minutes	10 Minutes	>15 Minutes
A. Ketamine 0.5%	100	0	0
B. Amitriptylline 0.05%	79.4	11.8	8.8
C. Guanethidine 0.05%	76.4	8.8	17.6
D. A + B	100	0	0
E. A + C	100	0	0
F. Placebo	0	0	2.9

Treatment	Duration of >50% Pain Relief (Patient Percentage)		
	1 Hour	2 Hours	3 Hours
A. Ketamine 0.5%	91.2	82.4	58.8
B. Amitriptylline 0.05%	52.9	50.0	32.4
C. Guanethidine 0.05%	14.7	8.8	2.9
D. A + B	97.1	97.1	97.1
E. A + C	94.1	88.2	82.4
F. Placebo	0	0	0

*5.9% developed minimal statistically significant pain relief.

2. ALLODYNIA

Treatment	Percentage Patients with >50% Pain Relief At 5 Minutes	At 2 Hours	At 3 Hours
A. Ketamine 0.5%	79.4	82.4	82.4
B. Amitriptylline 0.05%	8.8	11.8	5.9
C. Guanethidine 0.05%	0	0	0
D. A + B	88.2	91.2	91.2
E. A + C	79.4	85.3	85.3
F. Placebo	0	0	0

Treatment	Percentage Patients with 0 Pain Relief
A. Ketamine 0.5%	2.9
B. Amitriptylline 0.05%	47.1
C. Guanethidine 0.05%	67.6
D. A + B	0
E. A + C	2.9
F. Placebo	94.1*

Treatment	Time of Onset of Pain Relief (Patient Percentage) 5 Minutes	10 Minutes	>15 Minutes
A. Ketamine 0.5%	91.2	5.9	2.9
B. Amitriptylline 0.05%	35.3	2.9	58.8
C. Guanethidine 0.05%	17.6	8.8	73.5
D. A + B	100.0	0	0
E. A + C	91.2	5.9	2.9
F. Placebo	0	0	2.9

Treatment	Duration of >50% Pain Relief (Patient Percentage) 1 Hour	2 Hours	3 Hours
A. Ketamine 0.5%	82.4	82.4	82.4
B. Amitriptylline 0.05%	11.8	11.8	5.9
C. Guanethidine 0.05%	0	0	0
D. A + B	91.2	91.2	91.2
E. A + C	82.4	82.4	82.4
F. Placebo	0	0	0

*5.9% developed minimal statistically significant pain relief.

Topical Compositions Study: Summary of Results

Rest Pain	Onset of Pain Relief (Patient Percentage)			> 50% Pain Relief (Patient Percentage)			Duration of >50% Pain Relief (Patient Percentage)		
	5 Min.	10 Min.	>15 Min.	5 Min.	2 Hours	3 Hours	1 Hour	2 Hours	3 Hours
A. Ketamine 0.5%	100	0	0	64.7	82.4	61.8	91.2	82.4	58.8
B. Amitriptylline 0.05%	79.4	11.8	8.8	32.4	50.0	32.4	52.9	50.0	32.4
C. Guanethidine 0.05%	76.4	8.8	17.6	5.9	8.8	2.9	14.7	8.8	2.9
A + B	100	0	0	82.4	97.1	97.1	97.1	97.1	97.1
A + C	100	0	0	79.4	88.2	82.4	94.1	88.2	82.4
Placebo	0	0	2.9	0	0	0	0	0	0

Allodynia	Onset of Pain Relief (Patient Percentage)			> 50% Pain Relief (Patient Percentage)			Duration of >50% Pain Relief (Patient Percentage)		
	5 Min.	10 Min.	>15 Min.	5 Min.	2 Hours	3 Hours	1 Hour	2 Hours	3 Hours
A. Ketamine 0. 5%	91.2	5.9	2.9	79.4	82.4	82.4	82.4	82.4	82.4
B. Amitriptylline 0.05%	35.3	2.9	58.8	8.8	11.8	5.9	11.8	11.8	5.9
C. Guanethidine 0.05%	17.6	8.8	73.5	0	0	0	0	0	0
A + B	100	0	0	88.2	91.2	91.2	91.2	91.2	91.2
A + C	91.2	5.9	2.9	79.4	85.3	85.3	82.4	82.4	82.4
Placebo	0	0	2.9	0	0	0	0	0	0

Discussion:

The following points warrant additional comment.

I. Significant Pain Relief And Duration Of Relief

A. Rest Pain

A total of 97% of the study patients achieved greater then a 50% reduction in their rest pain following application of lecithin matrix gel containing the combination of 0.5% ketamine plus 0.05% amitriptylline at two and three hours following application.

The 0.5% ketamine composition alone produced significant pain relief in 82% of patients at 2 hours and 62% at 3 hours.

The 0.05% guanethidine composition was effective only when combined with 0.5% ketamine, providing 88% of the patients with significant pain relief lasting two hours or more. 82% of these patients achieved greater than three hours of almost total pain relief.

The respective significant pain relief percentages for the 0.05% amitriptylline composition were 50% at 2 hours and 32% at 3 hours.

In those patients who had placebo topical composition applied, none demonstrated more than a 20% pain reduction at any of the test

measurement intervals, which did not meet the criteria of significant (>50%) pain relief.

The duration of the significant pain relief was 3 hours or more in 97% of the patients treated with 0.5% topical ketamine plus 0.05% ketamine.

This was compared to only 59% of patients with significant pain relief lasting 3 hours or more treated with 0.5% ketamine alone in a composition and 32% of patients treated with 0.05% amitriptylline alone in a composition.

B. Allodynia - (pain upon light touch)

Application of 0.5% ketamine alone resulted in 82% of these patients experiencing significant pain relief at two and three hours.

Adding 0.05% amitriptylline to ketamine was advantageous in that 91% of the patients experienced significant pain relief at two and three hours.

There was no apparent advantage to adding guanethidine to the ketamine since 85% of these patients reported significant pain relief at two and three hours an insignificant difference from the 82% with ketamine alone.

0.05% guanethidine alone and placebo compositions were statistically ineffective for relief of allodynia. None of these patients experienced significant pain relief.

Once developing a significant reduction of pain, 82% of the allodynia patients who were treated with the 0.5% ketamine or 0.5% ketamine plus 0.05% guanethidine compositions, maintained that level of pain relief for greater than three hours. However, 91% of patients treated with 0.5% ketamine plus 0.05% amitriptylline experienced three hours of significant pain relief. This compared to only 6% of patients treated with the 0.05% topical amitriptylline alone.

II. Onset of Significant Pain Relief

All of the rest pain and allodynia patients treated with 0.5% ketamine or 0.5% ketamine plus 0.05 % guanethidine or 0.05% amitriptylline experienced onset of significant pain relief within five minutes of application. 0.05% amitriptylline composition had a slower onset, with 80% of rest pain patients and only 35% of allodynia patients experiencing relief in the first five minutes after application of the topical composition. Onset of significant pain relief was over 15 minutes in 60% of the allodynia patients.

III. Statistical Analysis

Our analysis[1] revealed this treatment to be effective equally in diabetic peripheral neuropathy, idiopathic peripheral neuropathy, peripheral neuropathy in patients with AIDS, and patients with other mixed types of

[1] Bruce M. Frome, MD "Raw Data and Statistical Analysis from Clinical Trials Comparing Efficacy of Topical Compositions containing Therapeutically Active Agents on Relief of Sympathetically Mediated Pain". September 1995: Un-published paper.

pain, especially sympathetically mediated pain. No significant differences were found related to the age or sex of the patients.

Conclusions:

1. Topical compositions containing 0.5% ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, are effective for use in the treatment and relief of rest pain and allodynia due to nerve injury (SMP).

2. Topical compositions containing 0.05% amitriptylline, an example of an anticholinergic agent, are effective for use in the treatment and relief of rest pain but ineffective for treating allodynia secondary to nerve injury (SMP).

3. Topical compositions containing 0.05% guanethidine, a sympathetic blocking agent, are effective in reducing the intensity of rest pain due to nerve energy (SMP). However, 0.05% guanethidine was ineffective in the relief of the allodynia type pain due to nerve injury.

4. Topical compositions containing both 0.5% ketamine and 0.05% amitriptylline proved to be the most effective for the relief of pain due to nerve injury (SMP) after comparing efficacy of 0.5% topical ketamine, 0.05% topical guanethidine, and 0.05% topical amitriptylline, individually and in combinations. Almost all patients treated with the 0.5% ketamine/0.05% amitriptylline composition combination in lecithin composition exhibited

rapid and almost complete relief of all pain that lasted greater than three hours.

5. Administered separately, 0.5% topical ketamine compositions were the most effective offering all patients rapid, prolonged and significant pain relief from pain due to nerve injury (SMP). 0.05% amitriptylline topically administered separately in a composition was less effective than ketamine. 0.05% topical guanethidine administered separately in a composition was the least effective of the three active ingredients studied.

6. Time of onset of significant pain relief was less than five minutes in almost all of patients studied when 0.5% topical ketamine was part of the formula. Duration of onset was longer when 0.05% topical amitriptylline was used separately without topical ketamine. 0.05% topical guanethidine compositions had the longest onset of action over fifteen minutes after topical application, in the majority of patients studied

7. No side effects attributable to the topical compositions were demonstrated by any of the patients studied. Nevertheless, low blood pressure or a history of vascular headaches is a relative contraindication to the use of topical guanethidine.

8. Due to its convenience, simplicity of self application, lack of side effects, ease of preparation, and low cost, the use of topical regional

treatment is a valuable addition to the treatment protocol of nerve injury pain (SMP).

CONCLUSIONS, RAMIFICATIONS, AND SCOPE

Accordingly, it can be seen that we have provided a method of preparation of compositions resulting in a relatively simple method of treating pain, regardless of cause, and including all forms of peripheral neuropathy, in patients of either sex. The method of preparation utilizes therapeutically active agents prepared in suitable bases then applied periodically to the skin areas affected by such pain.

The therapeutically active agents include three classes of drugs: NMDA receptor antagonists, anticholinergic agents and sympathetic blocking agents, as well as combinations of two or more of these. The method provides a rapid onset of significant pain relief which lasts significantly greater than 2 hours in the patients studied. The topical compositions are generally non-toxic and have minimal non-serious side effects. Specifically, no habit forming or addicting medications are used. The topical compositions can be self administered safely at home or administered by a care giver in any locale.

Although the description above contains specific examples of ketamine, an NMDA antagonist, used at its most effective concentration of 0.5%, it was

also found in clinical trials to be safe and effective when prepared with the dosage between 0.05% to 2% of the topical composition.

Although the description above contains specific examples of amitriptylline, an anticholinergic agent, used at its most effective concentration of 0.05%, it was also found in clinical trials to be safe and effective when prepared with the dosage between 0.01% to 0.1% of the topical composition.

Although the description above contains specific examples of guanethidine. a sympathetic blocking agent, used at its most effective concentration of 0.05%, it was also been found in clinical trials to be safe and effective when prepared with the dosage between 0.01% to 0.1% of the topical composition.

Although the description above contains many specificies, these should not be construed as limiting the scope of the invention but as merely providing illustrations of some of the presently preferred embodiments of this invention. Various other embodiments and ramifications are possible within its scope.

Thus the scope of the invention should be determined by the appended claims and their legal equivalents, rather than by the examples given.

I CLAIM

1. A method for the preparation of a topical composition containing therapeutically active agent or agents used for treatment of pain especially in patients diagnosed with sympathetically mediated pain.

2. The method of claim 1 whereby one or more therapeutically active agents is selected from the class of NMDA receptor antagonists, for example, but not limited to, ketamine.

3. The method of claim 1 whereby one or more therapeutically active agents is selected from the class of anticholinergic agents, for example, but not limited to, one or more tricyclic antidepressants, including, but not limited to, amitriptylline.

4. The method of claim 1 whereby one or more therapeutically active agents is selected from the class of sympathetic blocking agents, for example, but not limited to, guanethidine.

5. The method of claim 1 whereby a therapeutically active agent is selected from the class of NMDA antagonists, for example, but not limited to, ketamine, is combined with another therapeutically active agent selected from the class of anticholinergic agents, for example, but not limited to, one or more tricyclic antidepressants, such as, but not limited to, amitriptylline.

6. The method of claim 1 whereby one or more therapeutically active agents selected from the class of NMDA receptor antagonists, for example, but not limited to, ketamine, is combined with another therapeutically active agent selected from the class of sympathetic blocking agents, such as, but not limited to, guanethidine.

7. The method of claim 1 whereby one or more therapeutically active agents is prepared in a topical composition base containing as its principle ingredient one or more standard topical cosmetic or topical medicinal bases, for example, but not limited to, lecithin composition, cocoa butter, aloe vera gel, aguafor, petroleum jelly and/or a standard cold cream.

8. The method of claim 7 whereby one or more therapeutically active agents from the class of NMDA receptor antagonist, for example ketamine, is prepared in a topical composition base containing as its principle ingredient one or more standard topical cosmetic or topical medicinal bases, for example, but not limited to, lecithin composition, aloe vera gel, cocoa butter, aquafor, petroleum jelly, and/or a standard cold cream.

9. The method of claim 7 whereby one or more therapeutically active agents from the class of anticholinergic agents, for example amitriptylline, is prepared in a topical composition base containing as its principle ingredient one or more standard topical cosmetic or topical medicinal bases, for example, but not limited to, lecithin composition, aloe vera gel, cocoa butter, aquafor, petroleum jelly, and/or a standard cold cream.

10. The method of claim 7 whereby one or more therapeutically active agents from the class of sympathetic blocking agents, for example guanethidine, is prepared in a topical composition base containing as its principle ingredient one or more standard topical cosmetic or topical medicinal bases, for example, but not limited to, lecithin composition, aloe vera gel, cocoa butter, aquafor, petroleum jelly, and/or a standard cold cream.

11. The method of claim 7 whereby one or more therapeutically active agents from the class of NMDA receptor antagonist, for example ketamine, combined with one or more therapeutically active agents from the class of anticholinergic agents such as the tricyclic antidepressants, for example, amitriptylline, is prepared in a topical composition base containing as its principle ingredient one or more standard topical cosmetic or topical medicinal bases, for example, but not limited to, lecithin composition, aloe vera gel, cocoa butter, aquafor, petroleum jelly, and/or a standard cold cream.

12. The method of claim 7 whereby one or more therapeutically active agents from the class of NMDA receptor antagonist, for example ketamine, combined with one or more therapeutically active agents from the class of sympathetic blocking agents, for example, guanethidine, is prepared in a topical composition base containing as its principle ingredient one or more

standard topical cosmetic or topical medicinal bases, for example, but not limited to, lecithin composition, aloe vera gel, cocoa butter, aquafor, petroleum jelly, and/or a standard cold cream.

13. The method of claim 7 whereby one or more therapeutically active agents, prepared in the topical composition is therapeutically used by topical application for the establishment of pain relief in persons experiencing pain, especially in those persons diagnosed with sympathetically mediated pain (SMP).

14. The method of claim 13 whereby one or more therapeutically active agents, prepared in the topical composition is selected from the class of NMDA receptor of pain relief in persons experiencing pain, especially in those persons diagnosed with sympathetically mediated pain (SMP).

15. The method of claim 13 whereby one or more therapeutically active agents, prepared in the topical composition is selected from the class of anticholinergic agents such as the tricyclic antidepressants, for example, amitriptylline, and is therapeutically used for pain relief in persons experiencing pain, especially in those persons diagnosed with sympathetically mediated pain (SMP).

16. The method of claim 13 whereby one or more therapeutically active agents, prepared in the topical composition is selected from the class of sympathetic blocking agents, for example, guanethidine, and is

therapeutically used for pain relief in persons experiencing pain, especially in those persons diagnosed with sympathetically mediated pain (SMP).

17. The method of claim 13 whereby one or more therapeutically active agents, prepared in the topical composition is selected from the class of NMDA receptor antagonists, for example, ketamine, combined with one or more therapeutically active agents from the class of anticholinergic agents such as the tricyclic antidepressants, for example, amitriptylline, is therapeutically used for pain relief in persons experiencing pain, especially in those persons diagnosed with sympathetically mediated pain (SMP).

18. The method of claim 13 whereby one or more therapeutically active agents, prepared in the topical composition is selected from the class of NMDA receptor antagonists, for example, ketamine, combined with one or more therapeutically active agents from the class of sympathetic blocking agents, for example, guanethidine, is therapeutically used for pain relief in persons experiencing pain, especially in those persons diagnosed with sympathetically mediated pain (SMP).

19. The method of claim 13 whereby one or more therapeutically active agents selected from the class of NMDA receptor antagonists, for example, ketamine, is safe and therapeutically effective for the relief of pain when prepared with the dosage of the therapeutically active agent measured at certain concentrations of the topical composition.

20. The method of claim 13 whereby one or more therapeutically active agents selected from the class of anticholinergic agents such as the tricyclic antidepressants, for example, amitriptylline, is safe and therapeutically effective for the relief of pain when prepared with the dosage of the therapeutically active agent measured at certain concentrations of the topical composition.

21. The method of claim 13 whereby one or more therapeutically active agents selected from the class of sympathetic blocking agents, for example, guanethidine, is safe and therapeutically effective for the relief of pain when prepared with the dosage of the therapeutically active agent measured at certain concentrations of the topical composition.

22. The method of claim 13 whereby one or more therapeutically active agents selected from the class of NMDA receptor antagonists, for example, ketamine, combined with one or more therapeutically active agents from the class of anticholinergic agents such as the tricyclic antidepressants, for example, amitriptylline, is safe and therapeutically effective for the relief of pain when prepared with the dosage of the therapeutically active agent measured at certain concentrations of the topical composition.

23. The method of claim 13 whereby one or more therapeutically active agents selected from the class of NMDA receptor antagonists, for example, ketamine, combined with one or more therapeutically active agents from the

class of sympathetic blocking agents, for example, guanethidine, is safe and therapeutically effective for the relief of pain when prepared with the dosage of the therapeutically active agent measured at certain concentrations of the topical composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/14856

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/13, 31/135, 31/33
US CL :514/183, 659, 646
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/183, 659, 646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Abstract, Volume 42, Number 8, issued August 1993, Shimoda et al., "Transdermal application of 10% lidocaine-gel for management of pain associated with herpes zoster", pages 1171-6, Department of Anesthesiology, Kumamoto Rosai Hospital, Yatsushiro. Masui, see entire abstract.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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